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EXAMINER

MITCHELL, GREGORY W

ART UNIT	PAPER NUMBER
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1617

DATE MAILED: 11/30/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

## Office Action Summary

Application No.

09/914,708

Applicant(s)

BOYD, MICHAEL R.

Examiner

Gregory W Mitchell

Art Unit

1617

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --  
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

### Status

- 1) ☒ Responsive to communication(s) filed on 17 September 2004.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

### Disposition of Claims

- 4) ☒ Claim(s) 1-31 is/are pending in the application.
- 4a) Of the above claim(s) 18-30 is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 1-17 and 31 is/are rejected.
- 7) ☒ Claim(s) 1-17 and 31 is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

### Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

### Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some \* c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
  - ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- \* See the attached detailed Office action for a list of the certified copies not received.

### Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)  
Paper No(s)/Mail Date \_\_\_\_\_
- 4) ☐ Interview Summary (PTO-413)  
Paper No(s)/Mail Date \_\_\_\_\_
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☐ Other: \_\_\_\_\_

### **DETAILED ACTION**

This Office Action is in response to the remarks filed on September 17, 2004. Claims 1-31 are pending. Claims 18-30 have been withdrawn from consideration as being drawn to an unelected invention. Claims 1-17 and 31 are examined herein.

#### ***Priority***

This Application is a national stage application of PCT/US00/05582, filed March 2, 2000, which claims priority to US Provisional Applications 60/122,953 and 60/169,564, filed March 5, 1999 and December 8, 1999, respectively. Applicant's priority is acknowledged.

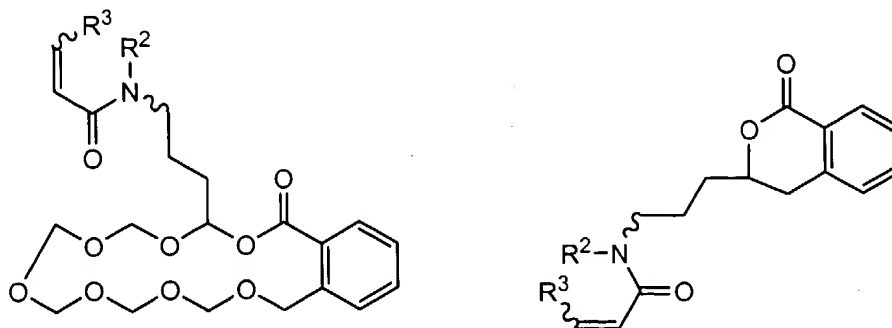
#### ***Election/Restrictions***

Applicant's election with traverse of Group I in the reply filed on September 17 is acknowledged. The traversal is on the ground(s) that all groups share a special technical feature. This is not found persuasive for the reasons set forth in the Office Action dated June 16, 2004 and those below.

Applicant argues that the compounds of all groups should be examined together because they have "a common structural feature that accounts not only for a significant portion of the molecule, but also plays an important role in biological activity." These arguments are not persuasive because it is Examiner's position that the compounds do not share a common core. For example, the core of Group I is a carbocyclic lactone and the core of Group II is a nitrogen containing heterocycle. Furthermore, it is

Art Unit: 1617

Examiner's position that a compound of formula I comprising a polymethylene glycol Z segment does not share a common core with an isochroman-1-one – see below:



It is also noted that Groups I-V lack unity of invention with Groups VI-X because the scope of the composition claims of Groups VI-X are not commensurate with the scope of the compositions used in the method claims of Groups I-V. Accordingly, Groups I-V lack unity with Groups VI-X.

The requirement is still deemed proper and is therefore made **FINAL**.

### ***Claim Objections***

Claims 1-17 and 31 are objected to as containing non-elected subject matter.

### ***Claim Rejections - 35 USC § 112***

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 3-8, 15 and 16 are rejected under 35 U.S.C. 112, first paragraph, because the specification does not reasonably provide enablement for the **prevention**

of a condition treatable by the inhibition of vacuolar-type (H<sup>+</sup>)-ATPase. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

The instant specification fails to provide information that would allow the skilled artisan to fully practice the instant invention without **undue experimentation**. Attention is directed to *In re Wands*, 8 USPQ2d 1400 (CAFC 1988) at 1404 where the court set forth the eight factors to consider when assessing if a disclosure would have required undue experimentation. Citing *Ex parte Forman*, 230 USPQ 546 (BdApl 1986) at 547, the court recited eight factors:

(1) the nature of the invention; (2) the state of the prior art; (3) the relative skill of those in the art; (4) the predictability or unpredictability of the art; (5) the breadth of the claims; (6) the amount of direction or guidance presented; (7) the presence or absence of working examples; and (8) the quantity of experimentation necessary.

**(1) The Nature of the Invention:**

The invention is drawn to a method for the prevention or treatment of a condition treatable by the inhibition of vacuolar-type (H<sup>+</sup>)-ATPase with a composition comprising a compound of formula I of the instant invention.

**(2) Breadth of the Claims:**

The complex nature of the subject matter of this invention is greatly exacerbated by the breadth of the claims. The term "prevention" encompasses prevention in both

mammals at risk for any condition treatable by the inhibition of vacuolar-type (H<sup>+</sup>)-ATPase as well as those that would not normally be expected to have such a condition. Accordingly, the term "prevention" indicates a claim whereby those normally not at risk for a condition treatable by the inhibition of vacuolar-type (H<sup>+</sup>)-ATPase would be prevented from ever developing such a condition.

**(3) Guidance of the Specification:**

The guidance of the specification as to the prevention of a condition treatable by the inhibition of vacuolar-type (H<sup>+</sup>)-ATPase is completely lacking. The specification only provides evidence that specific compounds of formula I are capable of inhibiting vacuolar-type (H<sup>+</sup>)-ATPase in three types of cells; no evidence of prevention is provided (Table 9, page 90). It is also noted that Applicant has only provided IC<sub>50</sub> values for the inhibition and does not provide any concentration at which complete inhibition of vacuolar-type (H<sup>+</sup>)-ATPase is achieved. Furthermore, Applicant fails to specifically point out a population in which prevention is to occur.

**It is also noted that the plain language of the claim appears to indicate that the prevention aspect of the claim is not enabled. Examiner respectfully points out that the condition addressed is a condition *treatable* by the inhibition of vacuolar-type (H<sup>+</sup>)-ATPase, not a condition *preventable* by the inhibition of vacuolar-type (H<sup>+</sup>)-ATPase.**

**(4) Working Examples:**

As stated above, Applicant does not provide any working examples. Nor does Applicant even provide any evidence of vacuolar-type (H<sup>+</sup>)-ATPase being completely inhibited.

**(5) State of the Art:**

The state of the art regarding the treatment of *specific* conditions treatable by the inhibition of vacuolar-type (H<sup>+</sup>)-ATPase is high. The state of the art regarding the prevention of conditions treatable by the inhibition of vacuolar-type (H<sup>+</sup>)-ATPase *general* is underdeveloped, however.

Reasonable guidance with respect to preventing a disorder relies on quantitative analysis from defined populations that have been successfully pre-screened and are predisposed to particular types of disorder. This type of data might be derived from widespread genetic analysis, family histories, etc. For example, Applicant lists a diverse group of conditions preventable by the administration of the compounds of formula I, e.g. urinary acidification, bone resorption, the acrosomal acid secretion, cellular proliferation, angiogenesis, tumor cell invasiveness, metastasis, and drug resistance. It would be difficult to predict the population of patients who may develop any such condition. The essential element towards the validation of a preventive therapeutic is the ability to test the drug on subjects monitored in advance of any condition associated with the inhibition of vacuolar-type (H<sup>+</sup>)-ATPase and *link* those results with subsequent confirmation of the presence or absence of the disorder. This irrefutable link between antecedent drug and subsequent knowledge of the prevention of the disorder is the essence of a valid preventive agent. Further, a preventive administration also must

assume that the therapeutic will be safe and tolerable for anyone susceptible to the disease.

**(6) Predictability of the Art:**

As discussed above, it is difficult to predict in which population any condition treatable by the inhibition of vacuolar-type (H<sup>+</sup>)-ATPase will arise. Accordingly, it is difficult to predict to whom to administer the agents of the instant invention for the prevention of such a condition. It is well established that "the scope of enablement varies inversely with the degree of unpredictability of the factors involved." See *In re Fischer*, 427 F.2d 833, 839 (1970).

Since there is no defined patient population, it would be necessary to administer the composition to the population at large in order to achieve the prevention of the claimed conditions. In order to administer the agent to the population at large, one would need to consider the therapeutic effects, side effects and especially serious toxicity that may be generated by drug-drug interactions when and/or after administration to a host (e.g., a human) an compound of the instant invention.

**(7) The Quantity of Experimentation Necessary:**

As discussed above, the specification fails to provide sufficient support for determining all mammals susceptible to any condition treatable by the inhibition of vacuolar-type (H<sup>+</sup>)-ATPase in order to allow one of ordinary skill in the art to be capable of administering to a population the compounds of the instant invention for the *prevention* of all conditions treatable by the inhibition of vacuolar-type (H<sup>+</sup>)-ATPase in general. As a result, one of skill in the art would be forced to perform an exhaustive

search for the population of mammals that will develop any such condition and, thereby, use the instant invention.

*Genetech*, 108 F.3d at 1366 states that "a patent is not a hunting license. It is not a reward for search, but compensation for its successful conclusion" and "[p]atent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable."

Accordingly, the claims are evaluated as being a method of treatment; the method of prevention is not considered.

### ***Claim Rejections - 35 USC § 112***

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-17 and 30 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the treatment of specific conditions treatable by the inhibition of vacuolar-type (H<sup>+</sup>)-ATPase, such as those conditions treatable by the inhibition of vacuolar-type (H<sup>+</sup>)-ATPase in osteoclastoma cells, human kidney cells and/or macrophage cells, with compounds of instant formula I, such as Salicylihalamide A and Lobatamide A, does not reasonably provide enablement for **any** condition treatable by the inhibition of vacuolar-type (H<sup>+</sup>)-ATPase with a compound of instant formula I. The specification does not enable any person skilled in the art to which it

pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

The instant specification fails to provide information that would allow the skilled artisan to fully practice the instant invention without ***undue experimentation***. Attention is directed to *In re Wands*, 8USPQ2d 1400 (CAFC 1988) at 1404 where the court set forth eight factors to consider when assessing if a disclosure would have required undue experimentation. Citing *Ex parte Forman*, 230 USPQ 546 (BdApls 1986) at 547, the court recited eight factors:

(1) the nature of the invention; (2) the state of the prior art; (3) the relative skill of those in the art; (4) the predictability or unpredictability of the art; (5) the breadth of the claims; (6) the amount of direction or guidance presented; (7) the presence or absence of working examples; and (8) the quantity of experimentation necessary.

(1). **The Nature of the Invention:**

The rejected claims are drawn to a method of treating any condition treatable by the inhibition of vacuolar-type (H<sup>+</sup>)-ATPase with a compound of instant formula I. In the specification, Applicant describes such conditions as including urinary acidification, bone resorption, the acrosomal acid secretion, cellular proliferation, angiogenesis, tumor cell invasiveness, metastasis, and drug resistance (pp. 2-3).

(2). **Breadth of the Claims:**

The complex nature of the subject matter of this invention is greatly exacerbated by the breadth of the claims. The claims encompass the treatment of a diverse series of conditions.

(3). **Guidance of the Specification:**

The guidance given by the specification as to how one would administer the claimed compounds to a subject in order to inhibit any type of “condition treatable by the inhibition of vacuolar-type (H<sup>+</sup>)-ATPase” is limited. Most of the guidance of the specification is drawn to an *in-vitro* test of vacuolar-type (H<sup>+</sup>)-ATPase inhibitory action by via the use of the NCI 60 cell-line testing procedure using only a selection of seven compounds, most of which have only minor variations (p. 86, Table 7 of Applicant's Specification). It is noted that the NCI 60 cell-line testing procedure is drawn to a method of determining efficacy versus cancer, a type of condition treatable by the inhibition of vacuolar-type (H<sup>+</sup>)-ATPase specifically excluded in the instant claims. In Example 6, Applicant specifically tests the inhibitory activities for salicylhalamide A and lobatamide A against vacuolar-type (H<sup>+</sup>)-ATPase derived human osteoclastoma cells, human kidney cells, and macrophage cells.

Applicant also teaches on page 40 of the specification that one skilled in the art would understand that “not all vacuolar-type (H<sup>+</sup>)-ATPase inhibitors will inhibit equally the vacuolar-type (H<sup>+</sup>)-ATPase activity present in different kinds or locations of intracellular organelles, or in different kinds of locations of plasma membranes, or in different kinds or locations of cells or tissues.” Applicant explains on pages 40-41 by saying, “... a given vacuolar-type (H<sup>+</sup>)-[ATPase] inhibitory compound may preferentially inhibit vacuolar-type (H<sup>+</sup>)-ATPase in one or more kind or location or intracellular organelle, plasma membrane, cell or tissue” and that “... compounds can be selected for particular applications based on preferential inhibition of one or more kind of

Art Unit: 1617

vacuolar-type (H<sup>+</sup>)-ATPase over another." Applicant fails, however, to provide any data, beyond that described above, regarding the specific vacuolar-type (H<sup>+</sup>)-ATPase inhibitory activities of the compounds claimed herein.

(4). **Working Examples:**

Applicant provides *in vitro* examples of vacuolar-type (H<sup>+</sup>)-ATPase inhibition but fails to provide any working examples of the inhibition of vacuolar-type (H<sup>+</sup>)-ATPase via administration to a patient (i.e. *in vivo*).

(5). **State of the Art:**

The state of the art is relatively high with regard to treating conditions treatable by the inhibition vacuolar-type (H<sup>+</sup>)-ATPase. It is noted, however, that Gagliardi et al. (*J. Med. Chem.*, 1998, 1568-1573) teaches that the treatment of conditions with vacuolar-type (H<sup>+</sup>)-ATPase inhibitors can be selective (Title). Gagliardi et al. teaches that the selective modulation of different vacuolar-type (H<sup>+</sup>)-ATPases is possible (pp. 1568-9). Accordingly, a compound capable of selective vacuolar-type (H<sup>+</sup>)-ATPase inhibition will not be able to treat a condition treatable by vacuolar-type (H<sup>+</sup>)-ATPase inhibition, in an intracellular organelle, plasma membrane, cell or tissue unrelated to said selective vacuolar-type (H<sup>+</sup>)-ATPase inhibition.

Gagliardi et al. also teaches that bafilomycin A is not selective for any particular type of vacuolar-type (H<sup>+</sup>)-ATPases, but that bafilomycin derivatives are capable of slight differential modulation of different vacuolar-type (H<sup>+</sup>)-ATPases and that, as stated above, vacuolar-type (H<sup>+</sup>)-ATPase inhibitors can selectively inhibit different V-ATPases (pp. 1568-9). It is also pointed out that Gagliardi et al. teaches that treatment of non-

Art Unit: 1617

selective vacuolar-type (H<sup>+</sup>)-ATPase inhibitors such as, bafilomycin A, leads to systemic alteration of cellular physiology and, ultimately, to death (p. 1568). Therefore, general vacuolar-type (H<sup>+</sup>)-ATPase inhibitors lead to death; and specific vacuolar-type (H<sup>+</sup>)-ATPase inhibitors are incapable of treating all types of conditions capable of being treated by general vacuolar-type (H<sup>+</sup>)-ATPase inhibitors.

(6). **Predictability of the Art:**

The invention is directed to the treatment of condition against which vacuolar-type (H<sup>+</sup>)-ATPase inhibition is effective, in general. It is well established that "the scope of enablement varies inversely with the degree of unpredictability of the factors involved," and physiological activity is generally considered to be an unpredictable factor. See *In re Fisher*, 427 F.2d 833, 839 (1970). As stated above vacuolar-type (H<sup>+</sup>)-ATPase inhibitors may be selective but Applicant has provided no evidence as to whether the compounds of the instant invention are general vacuolar-type (H<sup>+</sup>)-ATPase inhibitors or specific vacuolar-type (H<sup>+</sup>)-ATPase inhibitors. Accordingly, one of ordinary skill in the art would be unable to predict which specific vacuolar-type (H<sup>+</sup>)-ATPase inhibitors of the instant invention would be useful for the treatment a specific disorder treatable by vacuolar-type (H<sup>+</sup>)-ATPase inhibition.

(7). **The Quantity of Experimentation Necessary:**

In order to practice the claimed invention, one of skill in the art would have to first envision a compound, selected from the countless compounds encompassed by the claimed invention of Applicant, that would be effective at treating a condition against which the inhibition of vacuolar-type (H<sup>+</sup>)-ATPase is effective. One would then have to

Art Unit: 1617

envision a combination of an appropriate pharmaceutical carrier, a dosage for each compound, the duration of treatment, route of treatment, etc. and, in the case of human treatment, an appropriate animal model system for one of the claimed compounds. One would then need to test the combination in the model system to determine whether or not the combination is effective for treating said disease. If unsuccessful, which is likely given the lack of significant guidance from the specification or prior art regarding treatment of any specific disease with any specific compound, one of skill in the art would have to then either envision a modification of the first combination of pharmaceutical compound, compound dosage, duration of treatment, route of administration, etc. and appropriate animal model system, or envision an entirely new combination of the above and test the system again. If again unsuccessful, which is likely given the lack of significant guidance from the specification or prior art regarding treatment of said types of condition with compounds of Applicant's invention, the entire, unpredictable process would have to be repeated until successful. In order to practice Applicant's invention, it would be necessary for one to conduct the preceding experimentation for each type of disease encompassed by "a condition treatable by the inhibition of vacuolar-type (H<sup>+</sup>)-ATPase" because, as described above by Gagliardi et al., vacuolar-type (H<sup>+</sup>)-ATPase inhibitors can be selective and if they are not, they lead to systemic alteration of the cellular physiology and death. Therefore, it would require undue, unpredictable experimentation to practice the claimed invention to treat any such disease by administration of any one of the compounds within the claims.

*Genetech*, 108 F.3d at 1366 states that “a patent is not a hunting license. It is not a reward for search, but compensation for its successful conclusion” and “[p]atent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable.”

### ***Claim Rejections - 35 USC § 102***

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

Claims 1-4, 12-18 and 31 are rejected under 35 U.S.C. 102(a) as being anticipated by Boyd et al. (WO 99/05136).

Boyd et al. discloses a method of treating cancer by administering a pharmaceutical composition comprising a compound of formula (I) found therein (Abstract). Boyd et al. specifically discloses salicylihalamide A and salicylihalamide B as compounds useful in the method disclosed therein (p. 9). The effective amount of the compounds are disclosed to be that which provides an effective blood level of from  $10^{-11}$ - $10^{-7}$  M (p. 13).

It is Examiner's position that since there is no patient population specifically recited in the instant claims, the administration of a compound of formula (I) to a patient for the treatment of cancer will inherently treat a patient for a disease treatable by the inhibition of vacuolar-type (H<sup>+</sup>)-ATPase (e.g. the inhibition of intra-organellar

Art Unit: 1617

acidification of intracellular organelles, inhibition of urinary acidification, inhibition of bone resorption, treatment of osteoporosis, inhibition of fertility, inhibition of angiogenesis, etc.) because the administration of the same composition to the same patient population in the same dosage will inherently treat diseases treatable by the inhibition of vacuolar-type (H<sup>+</sup>)-ATPase whether or not that treatment was specifically disclosed in the prior art.

### ***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Claim 6 is rejected under 35 U.S.C. 103(a) as being unpatentable over Boyd et al. (WO 99/05136).

Boyd et al. applies as disclosed in the 35 USC 102 rejection of claims 1-4, 12-18 and 31, above. It is noted that Boyd et al. further teaches a method of treating cancer whereby any compound of formula I is administered (Abstract). Boyd et al. does not specifically teach the administration of a composition comprising a compound of formula I wherein the Z linker group is less than 7 atoms in length.

It would have been obvious to one of ordinary skill in the art to administer a composition comprising a compound of formula I of Boyd et al. wherein the Z linker was 6 atoms in length because it is a homologue of the disclosed compounds and a person

Art Unit: 1617

of ordinary skill in the art would have had an expectation of success in treating cancer with such a composition. It has been held that members of a homologous series must possess unexpected properties not possessed by the homologous compounds disclosed in the prior art. *In re Hass*, 141 F.2d 127, 60 USPQ 548 (CCPA 1944).

Claims 8-11 are rejected under 35 U.S.C. 103(a) as being unpatentable over Boyd et al. as applied to claims 1-4, 12-17 and 31 above, and further in view of Holt et al. (WO 93/18652) and Yamamoto et al. (*Cell Struct. Funct.* 1998, **23**, 33-42)

Boyd et al. applies as disclosed above. Boyd et al. further teaches a treatment of cancer comprising the administration of an additional anticancer agent (p. 11), but does not specifically teach an additional component to be administered in the treatment of cancer selected from the group consisting of bafilomycins and concanamycins.

Holt et al. teaches the administration of bafilomycins (ATPase inhibitors) for the inhibition of cancers (Abstract, p. 2).

Yamamoto et al. teaches that the V-ATPase inhibition activity of bafilomycin A<sub>1</sub> is related to its cause of autophagy in rat hepatoma cell lines (cancer) (Abstract; pp. 33-34 and 40). Yamamoto et al. also teaches the equivalence of the V-ATPase inhibition activities of bafilomycin A<sub>1</sub> and concanamycins (pp. 40-41).

It would have been obvious to one of ordinary skill in the art to substitute the additional anticancer agent of Boyd et al. with a bafilomycin of Holt et al. because, as taught by Holt et al., bafilomycins are known to be administered for the inhibition of cancer. One would have been motivated to substitute the generic anticancer agent of Boyd et al. with a bafilomycin because of an expectation of success in treating cancer,

Art Unit: 1617

as taught by Boyd et al. Furthermore, it would have been obvious to specifically use bafilomycin A<sub>1</sub> as the bafilomycin or to substitute the bafilomycin with concanamycin A in the treatment rendered obvious by Boyd et al. and Yamamoto et al. because (1) bafilomycin A<sub>1</sub> is a bafilomycin; (2) bafilomycin A<sub>1</sub> is taught by Yamamoto et al. to cause atophagy in cancer cells; (3) concanamycins are taught to be the functional equivalent of bafilomycin A<sub>1</sub> by Yamamoto et al.; and (4) concanamycin A is a concanamycin.

### ***Conclusion***

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Gregory W Mitchell whose telephone number is 571-272-2907. The examiner can normally be reached on M-F, 8 AM - 4 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreeni Padmanabhan can be reached on .. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).



**SREENI PADMANABHAN**  
SUPERVISORY PATENT EXAMINER